

1. A pharmaceutical dosage form of a skeletal muscle relaxant providing a modified release profile comprising a population of extended release (ER) beads,

wherein said ER beads comprise

an active-containing core particle (IR (immediate release) bead) comprising a skeletal muscle relaxant; and

an ER (extended release) coating comprising a water insoluble polymer membrane surrounding said core,

wherein said dosage form when dissolution tested using United States Pharmacopoeia Apparatus 2 (paddles @ 50 rpm) in 900 mL of 0.1N HCl at 37°C exhibits a drug release profile substantially corresponding to the following pattern:

after 2 hours, no more than about 40% of the total active is released;

after 4 hours, from about 40-65% of the total active is released

after 8 hours, from about 60-85% of the total active is released; and

after 12 hours, from about 75- 85% of the total active is released;

thereby providing therapeutically effective plasma concentration over a period of 24 hours to treat muscle spasm associated with painful musculoskeletal conditions in humans.

2. A pharmaceutical dosage form as defined in claim 1, wherein said skeletal muscle relaxant is selected from the group consisting of cyclobenzaprine, dantrolene, methocarbamol, metaxalone, carisoprodol, diazepam, pharmaceutically acceptable salts or derivatives thereof and mixtures thereof.

3. A pharmaceutical dosage form as defined in claim 2 wherein said skeletal muscle relaxant is cyclobenzaprine hydrochloride and said pharmaceutical dosage form provides a maximum blood plasma concentration (C_{max}) within the range of about 80% to 125% of about 20 ng/mL of cyclobenzaprine HCl and an AUC_{0-168} within the range of about 80% to 125% of about

- 5 740 ng·hr/mL and a T_{\max} within the range of 80% to 125% of about 7 hours following oral administration of a single 30 mg cyclobenzaprine HCl MR Capsule.
4. A pharmaceutical dosage form as defined in claim 3 wherein the adjusted mean ratio of CMR 30 mg/CMR 15 mg is greater than about 2 for each of AUC_{0-168} ($p < 0.001$), $AUC_{0-\infty}$ ($p < 0.001$), and C_{\max} ($p < 0.001$).
5. A pharmaceutical dosage form as defined in claim 1 further comprising an immediate release (IR) bead population, wherein said IR beads when tested in a USP Type 2 Apparatus at 50 rpm in 900 ml 0.1 N HCl at 37°C release at least about 70% of the active within 30 minutes.
6. A pharmaceutical dosage form as defined in claim 1, wherein said dosage form comprises only one extended release bead population.
7. A pharmaceutical dosage form as defined in claim 1, wherein said water insoluble polymer is selected from the group consisting of ethers and esters of cellulose, pH-insensitive ammonio methacrylic acid copolymers, and mixtures thereof.
8. A pharmaceutical dosage form as defined in claim 7, wherein said extended release coating further comprises a plasticizer.
9. A pharmaceutical dosage form as defined in claim 8, wherein said plasticizer is selected from the group of triacetin, tributyl citrate, tri-ethyl citrate, acetyl tri-n-butyl citrate, diethyl phthalate, dibutyl sebacate, polyethylene glycol, polypropylene glycol, castor oil, acetylated mono- and di-glycerides and mixtures thereof.
10. A pharmaceutical dosage form as defined in claim 1, wherein said water insoluble polymer membrane on the drug cores comprises from about 7% to 12% by weight of the coated beads.
11. A pharmaceutical dosage form as defined in claim 7, wherein said extended release coating further comprises a water soluble polymer selected from the group consisting of

methycellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose, polyethylene glycol polyvinylpyrrolidone and mixtures thereof.

12. A method for the preparation of an oral once-daily drug delivery system comprising a skeletal muscle relaxant, comprising the steps of:

- a. preparing an active-containing core to form IR beads;
- b. coating the IR beads with an extended release coating comprising a plasticized water insoluble polymer to form ER (extended release) beads; and
- c. filling capsules with ER beads and optionally IR Beads at a ratio from about 70:30 to 100:0;

wherein said dosage form when dissolution tested using United States Pharmacopoeia Apparatus 2 (paddles @ 50 rpm) in 900 mL of 0.1N HCl at 37°C exhibits a drug release profile substantially corresponding to the following pattern:

after 2 hours, no more than about 40% of the total active is released;

after 4 hours, from about 40-65% of the total active is released

after 8 hours, from about 60-85% of the total active is released; and

after 12 hours, from about 75- 85% of the total active is released.

13. The method of claim 12, wherein said step of preparing an active-containing core comprises coating a particle selected from the group consisting of non-pareil seeds, acidic buffer crystals and alkaline buffer crystals with a water soluble film-forming composition comprising a muscle relaxant.

14. The method of claim 13 wherein said water soluble film-forming composition further comprises a polymeric binder.

15. The method of claim 12, wherein said step of preparing an active-containing core comprises granulating and milling and/or extruding and spheronizing a polymer composition containing a muscle relaxant.

16. The method of claim 12, wherein said extended release coating on the drug cores comprises from about 7% to 12% by weight of the coated beads.

17. The method of claim 12, wherein said muscle relaxant is selected from the group consisting of cyclobenzaprine, dantrolene, methocarbamol, metaxalone, carisoprodol, diazepam, pharmaceutically acceptable salts or derivatives thereof and mixtures thereof.

18. The method of claim 12, wherein the muscle relaxant comprises cyclobenzaprine hydrochloride.

19. The method of claim 18 wherein said pharmaceutical dosage form provides a maximum blood plasma concentration (C_{max}) within the range of about 80% to 125% of about 20 ng/mL of cyclobenzaprine HCl, an AUC_{0-168} within the range of about 80% to 125% of about 740 ng·hr/mL and a T_{max} within the range of 80% to 125% of about 7 hours following oral
5 administration of a single 30 mg cyclobenzaprine HCl MR Capsule.

20. The method of claim 12 wherein said extended release coating further comprises a plasticizer selected from the group consisting of triacetin, tributyl citrate, tri-ethyl citrate, acetyl tri-n-butyl citrate, diethyl phthalate, dibutyl sebacate, polyethylene glycol, polypropylene glycol, castor oil and acetylated mono- and di-glycerides and mixtures thereof.

21. The method of claim 12, wherein said extended release coating comprises ethylcellulose plasticized with diethyl phthalate.

22. A method of providing a patient with an oral dosage form, which comprises administering to said patient a sufficient amount of a dosage form of claim 3 to provide a total dose of 15 or 30mg of cyclobenzaprine hydrochloride once a day.